REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 47-54 are in the case.

I. DOUBLE PATENTING

The obviousness-type double patenting rejection of claims 47-54 as allegedly unpatentable over claim 3 of U.S. Patent 6,020,322, remains in abeyance until the present application is otherwise in condition for allowance. At that time, consideration will be given as to whether or not to submit a Terminal Disclaimer.

II. THE 35 U.S.C. § 112, FIRST PARAGRAPH, REJECTION

Claims 47-54 remain rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to reasonably to convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention. The rejection is respectfully traversed.

At the outset, it is noted that the first paragraph of 35 USC 112 requires that the "specification shall contain a written description of the invention". As stated in Paragraph I of The Interim Guidelines for Examination of Patent Applications under The 35 USC 112 First Paragraph Written Description Requirement (June, 1998), the written description requirement has several policy objectives. The Guidelines state, in part:

> "[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed. Another objective is to put the public in possession of what the applicant claims as the invention....

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. This requirement of the Patent Act promotes the progress of the useful arts by ensuring that patentees adequately describe their inventions in their patent specifications for the benefit of the public in exchange for the right to exclude others from practicing the invention for the duration of the patent term."

The written description of the present application, beginning at page 7, reveals that the subject matter of claims 47-54 is described in a way which reasonably conveys to the skilled artisan that the inventors had possession of the invention at the time the application was filed. For example, at page 30, beginning at line 3, the specification states:

> "The compositions of the present invention may be administered to an animal either before or after exposure to **radiation, sunlight or mutagens**. The acyl derivative form of the deoxyribonucleosides provides an orally effective means for delivery of deoxyribonucleosides to tissues. These derivatives may also be given parenterally or topically. Administration of the derivatives avoids the problem of rapid catabolism by gastrointestinal, liver and plasma enzymes." (Emphasis added)

At page 32 beginning with the second complete paragraph, the specification states:

> "There are conditions **other than radiation damage** in which exogenous deoxyribonucleosides or derivatives thereof have useful therapeutic applications. (Emphasis added)
> Deoxyribonucleic acid has been used to accelerate wound cicatrization or healing, and also to accelerate liver regeneration in experimental animals. It is likely that in these situations, as well as in the situation where DNA is used to promote survival after irradiation of animals, the DNA is serving as a storage depot for deoxyribonucleosides, which gradually releases the deoxyribonucleotides, and deoxyribonucleosides during enzymatic degradation."

At page 34, beginning in the third complete paragraph, the specification states:

> "For treatment of radiation-induced cellular damage or sunburn, or to enhance wound healing, preferred dosages include amounts of the acyl derivatives equivalent to 10 to 1000 mg of 2'-deoxyadenosine, 10 to 1000 mg of 2'-deoxyguanosine, 10 to 1000 mg of 2'-deoxycytidine and 10 to 1000 mg of 2'-deoxythymidine. For example, the composition may comprise 13-1330 mg of 3',5'-diacetyl-2'-deoxyadenosine, 13-1310 mg of 3',3'-diacetyl-2'-deoxyguanosine, 14-1370 mg of 3',5'-diacetyl-2'-deoxycytidine and 14-1350 mg of 3',5'-diacetyl-2'-deoxythymidine. As is understood in the art, in calculating such dosages, the equivalent amount of the 2'-deoxyribnucleoside alone is considered, i.e., the acyl substituent and acid addition portion of any pharmaceutically acceptable salt are not included in the calculation."

Of particular relevance to claim 54 is the description at page 34 in the first complete paragraph, which states:

> "Compositions within the scope of the invention include those which contain mixtures of the acyl derivatives of the deoxyribonucleosides in amounts effective to achieve its intended purpose. Such compositions may contain 0 to 50 mole percent of the acyl derivative of deoxycytidine, 0 to 50 mole percent of the acyl derivative of deoxyguanosine, 0 to 50 mole percent of the acyl derivative of deoxythymidine and 0 to 50 mole percent of the acyl derivative of deoxyadenosine, with the proviso that the total content of the acyl deoxyribonucleosides adds up to 100 mole percent."

Dr. Von Borstel (a co-inventor) has also advised that it is known to persons skilled in the art that, while different classes of mutagens can damage DNA in different ways (ionizing radiation causes DNA strand breaks; ultraviolet radiation causes pyrimidine dimers; alkylating agents attach foreign chemical moieties to DNA bases; antimetabolites can cause base substitutions), regardless of the nature of DNA damage, a primary mechanism for repair involves excision of a segment of damaged DNA, including a margin of undamaged DNA, followed by resynthesis of the DNA using the intact, nonexcised strand as a template. The precursors for resynthesis are deoxyribonucleotides. Pools of deoxyribonucleosides in resting cells are very low.

When challenged with mutagens, cells have an immediate requirement for deoxyribonucleotides for DNA repair, which must be accomplished prior to the next round of cell division, at which time mutations are permanently fixed in the genome.

Treatment of cells with compounds of the invention prior to, during, or after, treatment with mutagens prevents permanent fixation of mutations and the cellular consequences of such mutations by providing deoxyribonucleosides as precursors for the deoxyribonucleotides required for DNA repair during the critical time period before cell division. A sudden requirement for deoxyribonucleotides is a universal feature of cells treated with mutagens, regardless of the chemical nature of the DNA damage that they induce. This is why the compounds of the invention are useful for treatment and prevention of DNA damaged caused by mutagens in general, and **not** just ionizing radiation. In addition to preventing permanent fixation of mutations, the compounds employed in the methods of the invention may also serve as "decoys" for classes of mutagens that attack DNA bases, since the those compounds also feature the same chemical bases.

The compounds used in the methods of the invention, acyl derivatives of deoxyribonucleosides, act as prodrugs of the deoxyribonucleosides. They serve to improve delivery and pharmacokinetics of deoxyribonucleosides, since the native, unmodified deoxyribonucleosides are rapidly degraded when administered systemically. The compounds used in the present method enable systemic delivery of deoxyribonucleosides.

Example 13 on pages 50-53 of the present application demonstrates that the compounds of the invention produce improved survival of mice treated with ionizing

radiation. In an experimental system in which cells in culture (for which there are no delivery barriers for use of free deoxyribonucleosides instead of the acyl derivatives of the invention) are exposed to DNA-damaging doses of two additional classes of mutagens (ultraviolet light or nitric oxide), treatment with supraphysiological concentrations of deoxyribonucleosides reduces the incidence of DNA strand breaks (see Example 8 of commonly owned U.S. patent 6,255,290). Likewise, as shown in Example 5 of U.S. patent 6,255,290, exogenous deoxyribonucleosides reduce the yield of DNA strand breaks in cells treated with oxybenzone plus ultraviolet radiation (oxybenzone is activated by UV exposure to cause free-radical mediated DNA damage). These observations support the contention that deoxyribonucleosides delivered *in vivo* by administration of compounds of the invention are useful in general for treatment of DNA damaged caused by mutagens other than, and in addition to, ionizing radiation.

It is clear, therefore, that the invention the inventors were in possession of, as of the filing date of the application, was not one limited to treatment of cellular damage caused only by ionizing radiation. Moreover, the specification places the public in possession of the claimed invention, thereby satisfying Paragraph I of The Interim Guidelines for Examination of Patent Applications (*supra*).

On page 2 of the Action, the Examiner has asserted that:

> "The breadth of the claims is such that cellular damage caused by any mutagenic substance may be prevented or treated."

The Examiner further states that:

> "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by functional characteristics sufficient to show the applicant was in possession of the claimed genus. There are a variety of mutagenic substances; base analog mutagens, alkylators, uv mutagenesis, nitrous acid, ICR compounds, etc. each with a certain degree of specificity. There is limited predictability in the art that any one compound or class of compounds is capable of preventing or treating cellular damage from a variety of mutagenic substances."

The Examiner's position appears to be that, because the applicants have not disclosed all, or at least a representative number of, mutagens which can cause cellular damage, the description is not in compliance with the statute. The Examiner's position is traversed.

The statute does not require disclosure of subject matter well known to persons of ordinary skill in the art to which the application pertains. Federal Circuit decisions emphasize that a "...patent need not disclose what is well known in the art..." *In re Wands*, 858 F.2d, 731, 735, 8 USPQ 2d 1400, 1402 (CAFC 1988). Indeed, a "patent need not teach, and preferably omits, what is well known in the art." *Spectra-Physics Inc. v. Coherent, Inc.*, 827 F.2d 1524,1534, 3 USPQ 2d 1737, 1743 (CAFC 1987).

In the present case, the applicants were not under an obligation to apprise the skilled reader of the details of all the mutagens which can give rise to cellular damage. That was well known in the art as of the filing date of the application. All that was required to satisfy the written description requirement, as noted earlier, was to "describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." The skilled reader, upon reading the present specification, would not reasonably conclude that the

description is limited only to treatment of radiation induced cellular damage or sunburn using the compounds of the invention.

The Examiner notes that the specification presents dosages for the treatment of radiation induced cellular damage or sunburn with the compounds of the invention (p.34), and that:

> "...the specification states that the acylated deoxyribonucleosides may prevent radiation induced cellular damage. However, a statement of a potential effect does not constitute a sufficient written description for prevention; moreover, the support in the specification is not adequate for the claim to the treatment or prevention of cellular damage caused by any mutagen."

In regard to the language "...may prevent...", it is presumed that the Examiner is referring to the paragraph beginning at the bottom of page 50 of the application. However, when that passage is read in its entirety through to page 53, it is clear that the compounds are effective for their intended purpose. Thus, at page 53 of the specification, beginning at line 7, it is stated:

> "It is apparent that the palmitoyl derivatives (8 micromoles administered once per day) are at least as effective in improving survival of irradiated mice as a threefold higher dose of di-O-acetyl nucleosides (8 micromoles administered three times per day)."

Thus, it appears that the Examiner is reading portions of the specification in isolation without looking and the disclosure as a whole. Clearly, the entire disclosure must be considered in determining compliance with the statute.

On page 3 of the Action, the Examiner states:

> "To provide adequate support to the breadth of the claims, Applicant would have to establish that over a period of time, a population of individuals subjected to a variety of the types of mutagenic substances cited above, were treated for or did not incur any cellular damage. The data presented shows mortality rates after

> exposure to gamma radiation which may be adequately correlative for the species of treating radiation induced cellular damage; however, this does not correlate to a prevention or treatment of cellular damage caused by any mutagen as broadly claimed."

The statutory written description requirement does not require patent applicants to establish data such as that quoted above, and the Examiner has not provided any legal support for such a contention. Indeed, as established in the case of *In re Marzocchi et al*; 169 USPQ 367, 369 (CCPA 1971):

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis in the original)

The Examiner has not provided any evidence in the record to challenge the objective truth of the present disclosure. Absent any such evidence, the rejection must be withdrawn.

The Examiner has asserted at the bottom of page 3 of the action that:

> "The term data in this case is actually synonymous with the applicant's demonstration that they (sic) were in possession of an invention wherein cellular damage was prevented for a broad class of mutagen species.....In the response the applicant does not provide any of these relevant species to constitute possession of the breadth of species encompassed by the term mutagen...."

In response, the Examiner is directed to the rebuttal arguments presented earlier in this response, to the effect that applicants were not under an obligation to provide details in the specification of information which was well known in the art as of the filing date of the application. The disclosure at page 30, beginning at line 3 indicates that the

compositions of the invention may be administered to an animal either before or after exposure to "radiation, sunlight **or mutagens**" (emphasis added). From this, the skilled reader is clearly placed in possession of the fact that the present invention extends to treatment or prevention of damage caused by **any** mutagen, not just sunlight or other radiation. Having said that, this was no requirement for the applicants to go further and list examples of mutagens well known to those in the art.

For all of the reasons discussed above, it is believed that the written description of the presently claimed invention satisfies 35 USC 112, first paragraph. Withdrawal of the rejection is respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:lfm
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100